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Review

Diet–Microbiota–Metabolite Interactions in Parkinson's Disease: Beyond Short-Chain Fatty Acids Toward Precision Nutrition

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Featured Application

This review provides a nutrition-centered framework for identifying diet-responsive microbial metabolic pathways and candidate metabolite targets as a basis for future hypothesis-testing toward microbiome-informed dietary strategies and precision nutrition in Parkinson's disease.

Abstract

Parkinson's disease (PD) is a heterogeneous neurodegenerative disorder in which gastrointestinal dysfunction and gut microbiota alterations may precede motor manifestations. Diet is a major modifiable determinant of microbial composition and metabolic activity and therefore shapes the production of metabolites involved in gut–brain communication. This review examines the diet–microbiota–metabolite axis in PD, with emphasis on microbial signals beyond short-chain fatty acids. We integrate evidence on tryptophan and aromatic amino acid catabolites, bile acids, biogenic amines, bacterial lipids, trimethylamine N-oxide, polyamines, and other diet-responsive metabolites, and discuss their relationships with intestinal barrier function, neuroinflammation, mitochondrial dysfunction, α-synuclein pathology, and epigenetic regulation. Metabolomic and multi-omics approaches are considered as tools for linking nutritional exposures to microbial function and host metabolic phenotypes, while accounting for biological matrix, medication, and disease stage. Particular attention is given to interactions among diet, gut microbial metabolism, and levodopa (L-DOPA) bioavailability, alongside probiotics, prebiotics, postbiotics, and food-first interventions. Current evidence provides a research framework for future hypothesis-testing toward microbiome-informed dietary strategies and precision nutrition, but causal inference remains limited by cross-sectional designs, heterogeneous analytical protocols, and insufficient dietary characterization.

Keywords: Parkinson's disease; nutrition; metabolism; gut microbiota; microbial metabolites; gut–brain axis; metabolomics; precision nutrition

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1. Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disorder worldwide, surpassed only by Alzheimer's disease [1–3]. The global number of people living with PD is projected to reach 25.2 million by 2050, representing a 112% increase compared with 2021 [4]. The disease is primarily characterized by the loss of dopaminergic neurons in the substantia nigra pars compacta (SNpc) [5–8] and by abnormal aggregation of α-synuclein (α-Syn) protein in Lewy bodies [2,3,5].

Clinically, PD manifests through both motor symptoms such as bradykinesia, muscular rigidity, resting tremor, and postural and gait disturbances [1,5,6] and a broad range of non-motor symptoms [2]. These non-motor features, including gastrointestinal dysfunction (e.g., constipation, delayed gastric emptying), pain, sleep disturbances, mental health issues, and olfactory loss, frequently appear many years or even decades before the onset of classical motor manifestations [1,2,5]. Constipation is a well-recognized prodromal feature of PD and may precede the onset of motor symptoms by more than a decade [9]. PD is now recognized as a multisystem disorder affecting both the central and peripheral nervous systems [5,10,11].

In recent years, increasing attention has been directed toward the role of the gut microbiota (GM), the diverse community of microorganisms inhabiting the intestine in the pathophysiology of PD [2,3,5,12]. Bidirectional communication along the microbiota–gut–brain axis has been implicated in PD pathophysiology [2,3,5,12]. This communication is mediated by microbial metabolites, neurotransmitters, the immune system, and afferent nerves, including the vagus nerve [2,13–15]. According to Braak's hypothesis, α-Syn pathology may originate in peripheral sites, including the gastrointestinal tract, and subsequently propagate to the central nervous system (CNS) through neural pathways such as the vagus nerve [5,6,16]. Human epidemiological studies of vagotomy provide additional, although not definitive, support for a potential gut-to-brain route of PD pathology. Large registry-based studies reported a reduced risk of subsequent PD after truncal vagotomy in selected long-term analyses, whereas overall vagotomy and selective vagotomy were not consistently associated with PD risk, indicating that these findings should be interpreted cautiously rather than as definitive proof of Braak's hypothesis [17,18]. This model supports the possibility of a gut-originating pathway in a subset of patients with PD rather than a universal mechanism of disease initiation. In some cases, α-Syn pathology in the enteric nervous system (ENS) may precede CNS neurodegeneration by many years [19]. Gut microbiota dysbiosis, characterized by alterations in microbial composition and functional capacity, is frequently reported in patients with PD [20–23]. Such dysbiosis may lead to increased intestinal permeability, chronic intestinal inflammation, and neuroinflammation within the CNS, thereby promoting α-Syn aggregation [7,12,13,24]. Moreover, lipopolysaccharide (LPS) derived from GM may modulate α-Syn aggregation [6,15,16,23,25]. The principal routes linking gut dysbiosis and altered microbial metabolic output to PD-relevant neuroinflammatory and neurodegenerative processes are summarized in Figure 1.

Despite substantial progress in understanding the role of GM in PD, particularly in the context of short-chain fatty acids (SCFAs), many aspects of the underlying pathomechanisms remain unclear [14]. The functional implications of numerous microbiota changes and their interactions with the host are still poorly understood. The list of relevant metabolites and metabolic pathways beyond SCFAs remains ambiguous and poses an ongoing research challenge. Furthermore, there is no clear definition of a "healthy microbiome" to differentiate microbiota associated with pathology from those supporting physiological function and to provide therapeutic targets. Additional challenges include difficulties in culturing many gut bacterial species and the incomplete annotation of their genomes, which hinders the understanding of their specific roles [14]. There is also concern about reverse causality, as most studies are conducted after PD diagnosis, and the translation of basic research findings to human studies remains limited [14,26].

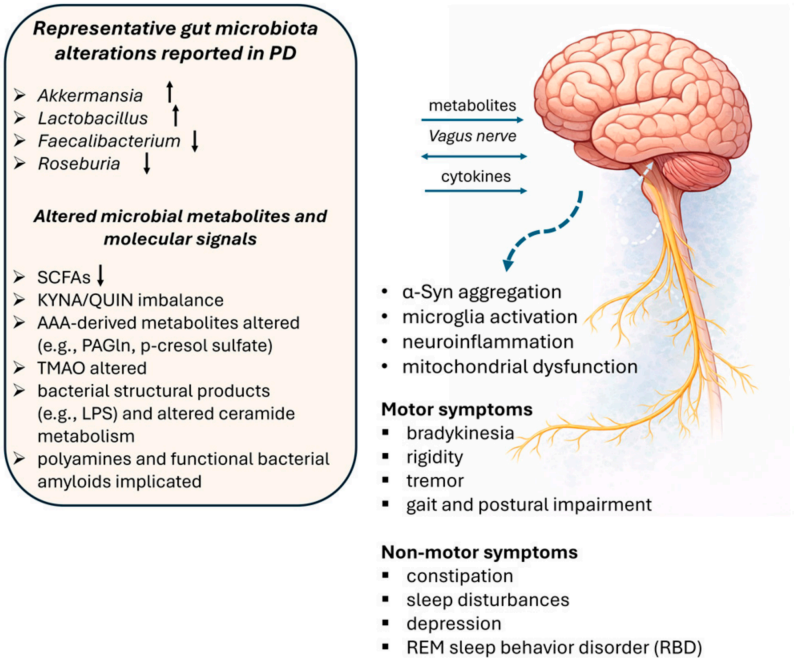


Figure 1. Representative gut microbiota alterations and microbiota–gut–brain axis mechanisms implicated in PD. Frequently reported changes in microbial composition and microbiota-associated metabolites or molecular signals may influence the central nervous system through circulating metabolites, cytokine-mediated immune signaling, and vagal pathways, contributing to α-synuclein aggregation, microglial activation, neuroinflammation, mitochondrial dysfunction, and motor and non-motor manifestations of PD. Upward (↑) and downward (↓) arrows indicate increases and decreases, respectively, in the abundance of the indicated microbial taxa or metabolite levels in PD compared with controls. Connecting arrows schematically indicate proposed routes of gut-to-brain signaling and do not imply established causality in humans.

Importantly, diet represents a major and modifiable upstream determinant of GM composition and function, shaping the spectrum of microbiota-derived metabolites relevant to PD. Dietary components including fermentable fiber, protein sources, fat quality, polyphenols, and micronutrients determine which microbial metabolic pathways are engaged, thereby influencing the production of SCFAs, aromatic amino acid catabolites, bile acids (BAs), vitamins, and neuroactive compounds. Consequently, nutritional exposures represent an important upstream layer in the diet–microbiota–metabolite–host axis, with downstream effects on intestinal barrier integrity, immune activation, mitochondrial function, and neuroinflammation. Framing microbiota-derived metabolites within this food-centered context is essential for translating mechanistic insights into scalable nutrition-based strategies for PD risk modification and adjunctive management. These mechanistic links are supported by clinical data showing that higher diet quality and fiber intake in PD patients are associated with increased abundance of putative butyrate-producing bacteria and reduced predicted inflammatory pathways [27].

Several recent reviews have addressed the relationships between nutrition, gut microbiota, and Parkinson's disease from complementary perspectives, including the impact of diet on the gut–brain axis, the influence of nutritional factors on gut microbial composition, and microbiome-based therapeutic approaches. These reviews have primarily emphasized dietary patterns, microbiota composition, clinical nutrition, or microbiome-targeted interventions. In contrast, the present review focuses specifically on diet-responsive microbiota-associated metabolic pathways and metabolites beyond SCFAs, integrating metabolomic evidence with microbial function to examine how nutritional exposures may shape host metabolic, neuroinflammatory, and neurodegenerative processes in PD [28–30].

The objective of this review is to explore in detail these emerging microbiota-derived signals that extend beyond the well-characterized SCFAs. We integrate current metabolomic data with microbiological insights to identify specific microorganisms and their metabolic pathways involved in the production of these metabolites. Furthermore, we synthesize mechanistic hypotheses linking diet, microbial metabolism, and PD-related pathways and highlight candidate diagnostic, prognostic, and stratification biomarkers, as well as potential therapeutic targets. Finally, we identify major research gaps and propose new experimental directions aimed at advancing our understanding of PD and fostering the development of precise, microbiome-targeted personalized therapeutic strategies.

2. Literature Search and Narrative Review Approach

This work was conducted as a narrative review to map and critically synthesize evidence on diet–microbiota–metabolite interactions in Parkinson's disease, with particular emphasis on metabolites beyond short-chain fatty acids, biological mechanisms, and implications for precision nutrition.

Relevant publications were identified through PubMed, Scopus, Web of Science, and Google Scholar using combinations of terms related to "Parkinson's disease", "gut microbiota", "metabolomics", "diet", "short-chain fatty acids", "tryptophan metabolism", "bile acids", "trimethylamine N-oxide", "aromatic amino acids", "microbial metabolites", and "precision nutrition". The review focused primarily on publications from 2013 to September 2026, with earlier foundational studies included where relevant. The last searches in PubMed, Scopus, Web of Science, and Google Scholar were each conducted in September 2026.

Titles and abstracts were assessed for relevance, with full-text assessment when necessary. Peer-reviewed English-language original research articles, reviews, and meta-analyses addressing human populations or relevant experimental models were considered. Conference abstracts, preprints, and non-English publications were excluded.

The narrative synthesis emphasized human metabolomic findings, dietary modulation, microbiota-associated metabolic pathways, and translational implications. Primary studies were preferentially cited for specific mechanistic and clinical claims. Conflicting findings were interpreted in relation to differences in biological matrix, disease stage, medication use, dietary exposure, cohort characteristics, and analytical methodology.

To improve transparency, Supplementary Table S1 maps the principal human studies by design, sample size, biological matrix, main findings, consideration of dietary and medication-related confounding, and proposed biomarker application. Study-level methodological support was assessed qualitatively by considering sample size, study design, confounder control, and independent validation. These assessments are descriptive and do not constitute a formal risk-of-bias assessment or GRADE evaluation. Human observational associations, interventional findings, genetic causal-inference analyses, and preclinical mechanisms were distinguished throughout the synthesis.

3. Nutrition as an Upstream Regulator of Gut Microbial Metabolism in Parkinson's Disease

To provide a structured overview of diet-microbiota-metabolite interactions relevant to PD, Table 1 summarizes the major dietary components, associated microbial functional groups, key metabolites, their reported alterations in PD, and translational nutritional implications.

Table 1. Dietary determinants of gut microbiota-associated metabolites relevant to Parkinson's disease. Upward (↑) and downward (↓) arrows indicate increases and decreases, respectively, in the levels or abundance of the indicated metabolites or microbial taxa in PD compared with controls. Arrows indicate general trends reported in the literature; inconsistent findings likely reflect differences in diet, disease stage, medication, and analytical approaches.

Dietary Component	Primary Food Sources	Microbial Functional Groups	Key Microbiota-Associated Metabolites	Direction of Change in PD	Mechanistic Effects Relevant to PD	Translational/Nutritional Implications
Fermentable dietary fiber	Whole grains, legumes, vegetables	SCFA-producing bacteria (Lachnospiraceae, *Faecalibacterium*)	Butyrate, propionate, acetate	↓ fecal SCFAs [5,31]	Epigenetic modulation (HDAC inhibition), support of gut barrier integrity, and anti-inflammatory effects, including induction of Tregs [1,6,32]	Dietary fiber enrichment and microbiota-targeted dietary strategies [6,32]
Tryptophan/ Protein	Red meat, dairy, eggs, seeds	Tryptophan-metabolizing bacteria (e.g., *Clostridium*, *Lactobacillus*)	IAA, IPA, IS, KYNA, QUIN	Heterogeneous; reduced circulating Trp and/or kynurenine reported in several studies [3,33–35]	AhR signaling by selected indole derivatives; excitotoxic and neurotoxic effects of QUIN; potentially neuroprotective effects of KYNA; oxidative and pro-inflammatory effects of IS [34,36–39]	Potential for metabolite-informed stratification and dietary modulation of protein quantity, source, and distribution; clinical relevance requires further validation [2,7,31,40]
Tyrosine and phenylalanine	Red meat, dairy, processed foods	Aromatic amino acid fermenters (*Enterococcus*, *Bacteroides*)	PAGln, PCS, PCG, phenylacetic acid	↑ circulating PCS and PAGln reported in several studies [41,42]	Associations with constipation, motor symptom severity, and RBD-related phenotypes; causal and mechanistic effects in humans remain incompletely established [41–43]	Potential use of aromatic amino acid–derived metabolites as gut-associated stratification markers; relevance to dietary protein source and microbial aromatic amino acid metabolism requires further validation [41,42,44,45]

Table 1. *Cont.*

Dietary Component	Primary Food Sources	Microbial Functional Groups	Key Microbiota-Associated Metabolites	Direction of Change in PD	Mechanistic Effects Relevant to PD	Translational/Nutritional Implications
Dietary fat/saturated-fat-rich dietary patterns	Red meat, processed foods, butter, high-fat animal-derived foods	BA–transforming bacteria (e.g., *Clostridium*, *Bilophila*)	Secondary bile acids, including DCA and LCA	Context-dependent alterations in primary and secondary bile acid profiles [46,47]	Modulation of intestinal barrier function and inflammatory signaling; potential effects on mitochondrial function and α-synuclein-related pathways [25,46,47]	Dietary fat quality and overall dietary pattern may influence bile acid pools and microbial bile acid transformation; the direction and magnitude of these effects appear to depend on disease stage, medication use, microbiota composition, and analytical approach [16,46–48]
Polyphenols	Berries, grapes, tea, pomegranate, nuts	*Gordonibacter, Ellagibacter*, and other polyphenol-transforming taxa	Urolithin A (UA)	↓ urolithin production reported in selected PD cohorts [49]	Antioxidant and mitochondrial effects; selected polyphenol-derived metabolites may also influence α-synuclein aggregation and inflammatory signaling [23,49,50]	Polyphenol-rich foods and functional-food strategies may represent diet-based approaches for modulating microbial metabolite production, although clinical evidence in PD remains limited [23,51,52]
Choline/L-carnitine	Red meat, dairy products, eggs, fish	TMA-producing gut bacteria	TMA and host-derived TMAO	↔ Inconsistent across biological matrices; both increased and decreased TMAO concentrations have been reported [24,53–56]	Potential pro-inflammatory effects and possible contribution to dopaminergic neurodegeneration; however, the clinical relevance of these mechanisms remains uncertain [24,53–56]	Potential for metabolite-informed patient stratification and dietary modulation of TMA precursor availability; clinical utility remains to be established [24,53–55]

Table 1. *Cont.*

Dietary Component	Primary Food Sources	Microbial Functional Groups	Key Microbiota-Associated Metabolites	Direction of Change in PD	Mechanistic Effects Relevant to PD	Translational/Nutritional Implications
Fermented foods	Yogurt, kefir, kimchi	Probiotic and fermentation-associated microorganisms, including selected *Lactobacillus* and *Bifidobacterium* spp.	SCFAs, selected B-group vitamins, vitamin K, and GABA	Not consistently established in PD; effects are likely strain-, product-, and host-dependent [25,33,57–60]	Potential support of intestinal barrier integrity, modulation of inflammatory signaling, and effects on microbial metabolite production and neuroactive signaling [25,33,58–60]	Fermented foods and probiotic-containing foods may represent food-based strategies for microbiota modulation, but PD-specific clinical evidence remains limited and requires further validation [25,57–60]

3-HPPA—3-(3-hydroxyphenyl)propionic acid; AhR—aryl hydrocarbon receptor; α-Syn—α-synuclein; BA—bile acid; DCA—deoxycholic acid; GABA—gamma-aminobutyric acid; HDAC—histone deacetylase; IAA—indole-3-acetic acid; IPA—indole-3-propionic acid; IS—indoxyl sulfate; KYNA—kynurenic acid; LCA—lithocholic acid; PAGln—phenylacetylglutamine; PCG—p-cresyl glucuronide; PCS—p-cresyl sulfate; PD—Parkinson's disease; QUIN—quinolinic acid; SCFA(s)—short-chain fatty acid(s); TMA—trimethylamine; TMAO—trimethylamine N-oxide; Trp—tryptophan; Tregs—regulatory T cells; UA—urolithin A.

Diet constitutes a major and modifiable upstream determinant of GM structure and function, thereby shaping the spectrum of microbiota-derived metabolites relevant to PD [3,12,32,61]. Unlike host genetic factors, dietary exposure is dynamic and cumulative, positioning nutrition as an important regulatory layer within the diet–microbiota–metabolite–host axis [15,25,48,62]. Within this framework, the GM acts as a diet-responsive metabolic interface, converting food-derived substrates into bioactive molecules capable of influencing intestinal, immune, metabolic, and neural processes implicated in PD pathophysiology [48].

From a functional perspective, distinct classes of dietary components selectively engage microbial metabolic pathways. Dietary fermentable carbohydrates serve as substrates for saccharolytic fermentation, driving the production of SCFAs such as acetate, propionate, and butyrate [25,48,62,63]. In contrast, microbial proteolytic fermentation generates amino acid-derived metabolites, including *p*-cresol and phenylacetylglutamine. Increased circulating levels of proteolytic microbial metabolites have been associated with altered gut function in PD [42]. Dietary amino acid availability may also influence these interactions: in a rotenone-induced mouse model of PD, a high-BCAA diet attenuated inflammation and improved motor and non-motor outcomes [64]. Dietary fat quality further modulates microbial metabolism by shaping BA pools, influencing BA– microbiota signaling via FXR and TGR5 pathways, and altering intestinal permeability and inflammatory tone [15,32,33,36]. Polyphenols and other food-derived phytochemicals, that escape digestion or absorption in the small intestine, undergo microbial biotransformation into low-molecular-weight phenolic metabolites with distinct mitochondrial, antioxidant, and anti-aggregatory activities [23,44,48–50].

These diet-driven microbial transformations generate metabolite profiles that act as downstream effectors linking nutritional exposure to host physiology. Diet-modulated microbiota-derived metabolites influence PD-relevant processes through multiple mechanisms, including regulation of gut barrier integrity, modulation of innate and adaptive immune responses, epigenetic control of gene expression, mitochondrial bioenergetics, and neurotransmitter synthesis and signaling [15,25,48,62]. Importantly, many of these metabolites, such as SCFAs, indole derivatives, secondary BAs, and selected polyamines exert pleiotropic effects across peripheral tissues and the CNS, either directly or via immune and neuroendocrine pathways [15,48,57].

Within this conceptual framework, variability in microbiota-derived metabolite profiles observed in PD should not be interpreted solely as disease-specific signatures, but rather as integrated readouts of long-term dietary patterns, microbial functional capacity, and host–microbiota interactions [12,31,48,63]. Differences in fiber intake, protein source and distribution, fat quality, and consumption of polyphenol-rich foods may contribute substantially to interindividual heterogeneity in metabolomic profiles and clinical phenotypes [15,48,62]. This perspective helps reconcile inconsistencies across studies and highlights the importance of accounting for dietary context when evaluating microbiota-associated biomarkers in PD [8,48,57].

These diet-responsive microbial pathways provide the mechanistic basis for the metabolite-focused and nutrition-oriented interventions discussed in the following sections.

3.1. Fermentable Carbohydrates, Dietary Fiber, and Short-Chain Fatty Acids

SCFAs, primarily acetate, propionate, and butyrate, are major end products of microbial fermentation of dietary fermentable carbohydrates, making habitual dietary fiber intake an important upstream determinant of their intestinal production and systemic availability. Differences in fiber quantity, physicochemical properties, and food-matrix complexity can differentially promote saccharolytic microbial pathways, thereby shaping both the composition and metabolic output of SCFA-producing communities. In PD, fiber-

dependent SCFA production may link long-term dietary patterns with intestinal barrier integrity, epigenetic regulation through histone deacetylase inhibition, and modulation of immune and neuroinflammatory signaling. Human studies most consistently indicate reduced fecal SCFA concentrations and depletion of several SCFA-producing bacterial taxa in PD, whereas circulating SCFA findings are less consistent across cohorts and biological matrices [5,31,40,65]. The pooled microbiome analysis by Kleine Bardenhorst et al. further supports a reproducible reduction in several taxa with SCFA-producing potential in PD [65]. Thus, the apparent discrepancy likely reflects differences between intestinal microbial production and circulating concentrations, as well as variation in dietary fiber intake, intestinal transit, medication use, analytical methodology, and the biological matrix examined.

While SCFAs represent the most extensively characterized class of microbiota-derived metabolites in PD, a broader spectrum of microbial metabolic signals has been investigated [66]. For example, Huh et al. used untargeted GC–MS metabolomics to identify alterations in colonic and plasma metabolic profiles in Proteus mirabilis-treated mice, including changes in galactose, fructose, and mannose metabolism [67]. To provide a structured synthesis of this complex metabolic landscape, Table 2 summarizes the major classes of gut microbiota-derived metabolites investigated in PD, encompassing both well-established compounds such as short-chain fatty acids and emerging molecular groups including tryptophan metabolites, aromatic amino acid derivatives, bacterial lipids, trimethylamine N-oxide (TMAO), polyamines, and functional bacterial amyloids (FuBA). For each class, representative metabolites, associated bacterial taxa, reported alterations in PD, described neurobiological effects, and potential therapeutic relevance are presented, enabling a comparative assessment of their biological and translational significance across key dimensions of PD pathophysiology, including neuroinflammatory signaling, mitochondrial function, epigenetic regulation, and α-synuclein pathology. Importantly, these metabolite groups differ not only in their mechanistic roles but also in the strength, consistency, and clinical relevance of the evidence linking them to disease onset, progression, and phenotypic heterogeneity.

To integrate this heterogeneous evidence base, Figure 2 provides a schematic representation of the major classes of microbiota-derived metabolites and their putative mechanisms of action in PD, synthesizing data from experimental, pre-clinical, and clinical studies. The strength and type of evidence vary across metabolite classes: SCFAs and selected tryptophan-derived compounds have been investigated mechanistically and in experimental interventions, aromatic amino acid derivatives are supported mainly by human observational findings, and evidence for bacterial amyloids remains predominantly preclinical. Evidence for bacterial structural and lipid-related signals combines experimental findings with limited human observational data.

From a nutritional perspective, diets rich in diverse fermentable fibers, including whole grains, legumes, vegetables, and selected fruits, represent a physiologically relevant approach to supporting endogenous SCFA production. More individualized strategies may additionally consider fiber type, gastrointestinal phenotype, including constipation-dominant PD, and individual microbiota composition to better account for interindividual variability in SCFA production and response.

Table 2. Major classes of gut microbiota-associated metabolites and molecular signals investigated in Parkinson's disease. Upward (↑) and downward (↓) arrows indicate increases and decreases, respectively, in the levels or abundance of the indicated metabolites or microbial taxa in PD compared with controls.

Metabolite Class	Representative Metabolites/ Signals	Associated Microbial Taxa/Source	Reported Alterations in PD	PD-Relevant Effects	Translational Relevance	Evidence Type/Strength
SCFA(s)	Butyrate, propionate, acetate	Lachnospiraceae; *Roseburia*; *Faecalibacterium*	↓ fecal SCFAs and depletion of several SCFA-producing taxa; plasma/serum findings remain inconsistent [5,31,40,65]	Gut-barrier integrity; immune and epigenetic regulation (HDAC inhibition); mitochondrial and glial effects [15,25,62,66]	Fiber/prebiotic strategies and SCFA-modulating probiotics; effects are context dependent [1,33,60,62]	Human associational + preclinical; limited human interventional evidence
Tryptophan metabolites	KYN, QUIN, KYNA, IAA, IS	*Bacteroides*; *Clostridium*; selected *Lactobacillus* spp.; *Demequina* [a] (genetic-proxy association with circulating Trp)	Heterogeneous; reduced Trp/kynurenine and altered indole/KP metabolites have been reported [11,31,34,35,37,38]	AhR and NMDA signaling; QUIN excitotoxicity; potentially neuroprotective effects of KYNA; oxidative and pro-inflammatory effects of IS [34,36,39]	Metabolite-informed stratification; die-tary/protein modulation and KP/Trp-targeted interventions remain investigational [31,34]	Human associational + preclinical
Aromatic amino acid derivatives	PAGln, PCS, PCG, phenylacetic acid	Aromatic amino acid-fermenting taxa, including *Clostridium* and *Ruminococcus*	↑ circulating PCS and PAGln reported in several cohorts; urinary alterations have also been reported for selected aromatic amino acid-derived metabolites [41–43]	Oxidative and pro-inflammatory signaling; associations with constipation, motor severity, and the proposed body-first phenotype [41–43]	Candidate stratification biomarkers; dietary and microbial targeting require further validation [41–43]	Human associational
Bacterial structural and lipid-related signals	LPS, PGN-derived fragments, ce-ramide/sphingolipid-related signals	Gram-negative bacteria; bacterial cell walls; sphingolipid-associated pathways	Altered ceramide metabolism has been reported in patients with PD [68]	Barrier dysfunction, innate immune signaling, α-Syn aggregation, neuroinflammation, and mitochondrial effects [6,14,16,25,35,69–75]	These pathways represent potential mechanistic and therapeutic targets, but no established PD-specific intervention currently targets LPS-, PGN-, or sphingolipid-related signaling [69,75]	Predominantly preclinical; limited human associational evidence

Table 2. *Cont.*

Metabolite Class	Representative Metabolites/ Signals	Associated Microbial Taxa/Source	Reported Alterations in PD	PD-Relevant Effects	Translational Relevance	Evidence Type/Strength
TMAO	TMA; host-derived TMAO	TMA-producing gut microbiota; subsequent host hepatic oxidation	Bidirectional observational findings: ↑ or ↓ depending on cohort and biological matrix; MR provides suggestive, but not definitive, evidence for effects on selected progression-related outcomes [13,24,53–56]	Potential pro-inflammatory and dopaminergic effects; clinical associations remain inconsistent [24,53–56]	Context-dependent metabolic correlate and candidate prognostic/stratification marker; diagnostic and predictive utility remains unestablished [13,24,54–56]	Human associational + Mendelian-randomization causal inference + preclinical
Polyamines	N8-acetylspermidine	Microbial and host polyamine metabolism	Higher serum N8-acetylspermidine concentrations in advanced compared with early-stage PD [76]	Cross-sectional association with disease stage; this finding does not establish a causal role in neuronal injury [76]	Candidate marker of disease stage; prognostic utility requires longitudinal validation	Human associational
FuBA	Curli and other bacterial amyloids	*E. coli* and other Enterobacteriaceae	Evidence linking functional bacterial amyloids to PD is predominantly experimental [3,16,31,72]	Potential promotion and cross-seeding of α-Syn aggregation, with possible modulation of inflammatory signaling [3,16,72]	Bacterial-amyloid-targeted strategies remain experimental; no established clinical intervention [3,16,31]	Predominantly preclinical

[a] The association between Demequina and circulating tryptophan is based on genetic-proxy evidence and does not demonstrate direct tryptophan-metabolizing activity of this genus. AAAs—aromatic amino acids; AhR—aryl hydrocarbon receptor; α-Syn—α-synuclein; CSF—cerebrospinal fluid; FuBA—functional bacterial amyloids; HDAC—histone deacetylase; IAA—indole-3-acetic acid; IS—indoxyl sulfate; KP—kynurenine pathway; KYN—kynurenine; KYNA—kynurenic acid; LPS—lipopolysaccharide; NMDA—N-methyl-D-aspartate; PAGln—phenylacetylglutamine; PCG—p-cresyl glucuronide; PCS—p-cresyl sulfate; PD—Parkinson's disease; PGN—peptidoglycan; QUIN—quinolinic acid; SCFA(s)—short-chain fatty acid(s); TMA—trimethylamine; TMAO—trimethylamine N-oxide; Trp—tryptophan. Evidence type reflects the predominant level of support for each metabolite class: human associational, human interventional/causal-inference, or preclinical evidence. Categories are intended as a qualitative summary and do not represent a formal GRADE assessment.

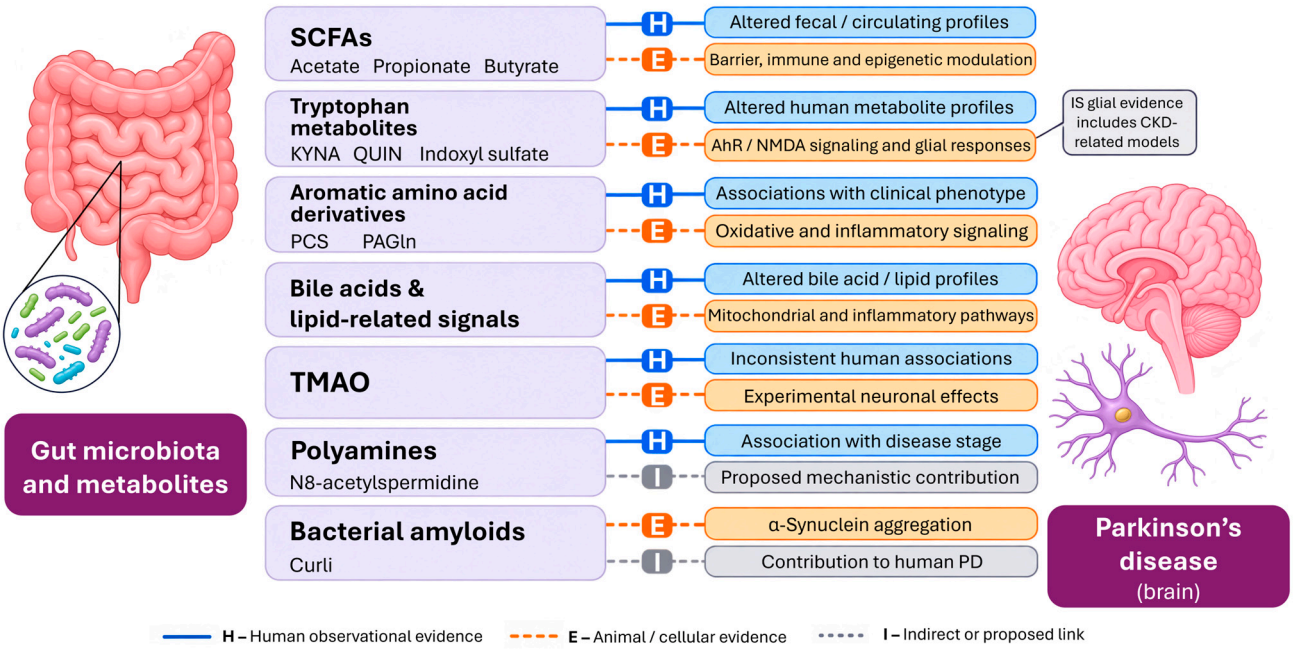


Figure 2. Major microbiota-derived metabolites and molecular signals implicated in PD. The scheme summarizes selected microbial and host–microbial co-metabolites, bacterial structural products, functional bacterial amyloids, and other molecular signals associated with PD-related pathophysiological processes. Abbreviations: SCFAs, short-chain fatty acids; KYNA, kynurenic acid; QUIN, quinolinic acid; IS, indoxyl sulfate; PAGln, phenylacetylglutamine; TMAO, trimethylamine N-oxide; FuBA, functional bacterial amyloids.

3.2. Dietary Protein, Tryptophan, and Aromatic Amino Acid Metabolism

Dietary tryptophan intake, determined by protein quantity, source, and digestibility, constitutes the primary substrate pool for microbial tryptophan metabolism in the gut. When dietary protein exceeds small-intestinal absorptive capacity or is embedded within complex food matrices, a greater proportion of tryptophan becomes available for microbial catabolism into indole derivatives and other bioactive metabolites, while microbiota–host interactions may indirectly modulate the host kynurenine pathway (KP). These diet-dependent microbial transformations link protein quality and dietary patterns to immune regulation, AhR signaling, and neuroinflammatory processes implicated in PD. Consequently, variability in tryptophan-derived metabolites observed in PD may reflect dietary exposure alongside disease- and treatment-related factors [1,3,31,40].

Dietary proteins can also release bioactive peptides during digestion, enzymatic hydrolysis, or fermentation. As summarized by Velarde-Salcedo et al. (2026), food-derived peptides represent an additional potential link between protein intake and diet–microbiome–brain signaling [77]. Selected arginine (Arg)-containing and tryptophan (Trp)-containing peptides have shown neuroprotective or cognition-related effects in experimental models [77,78]. However, amino acid composition alone does not establish neuropeptide activity, and these findings should not be interpreted as evidence of clinical efficacy in PD. Their relevance depends on peptide sequence, stability, bioavailability, and the experimental context.

The diet-sensitive partitioning of tryptophan among serotonergic, kynurenine, and microbiota-dependent indole routes provides an important mechanistic link between protein intake, microbial metabolism, and neuroactive signaling. These pathways are summarized in Figure 3 and discussed in detail in Section 4.2.

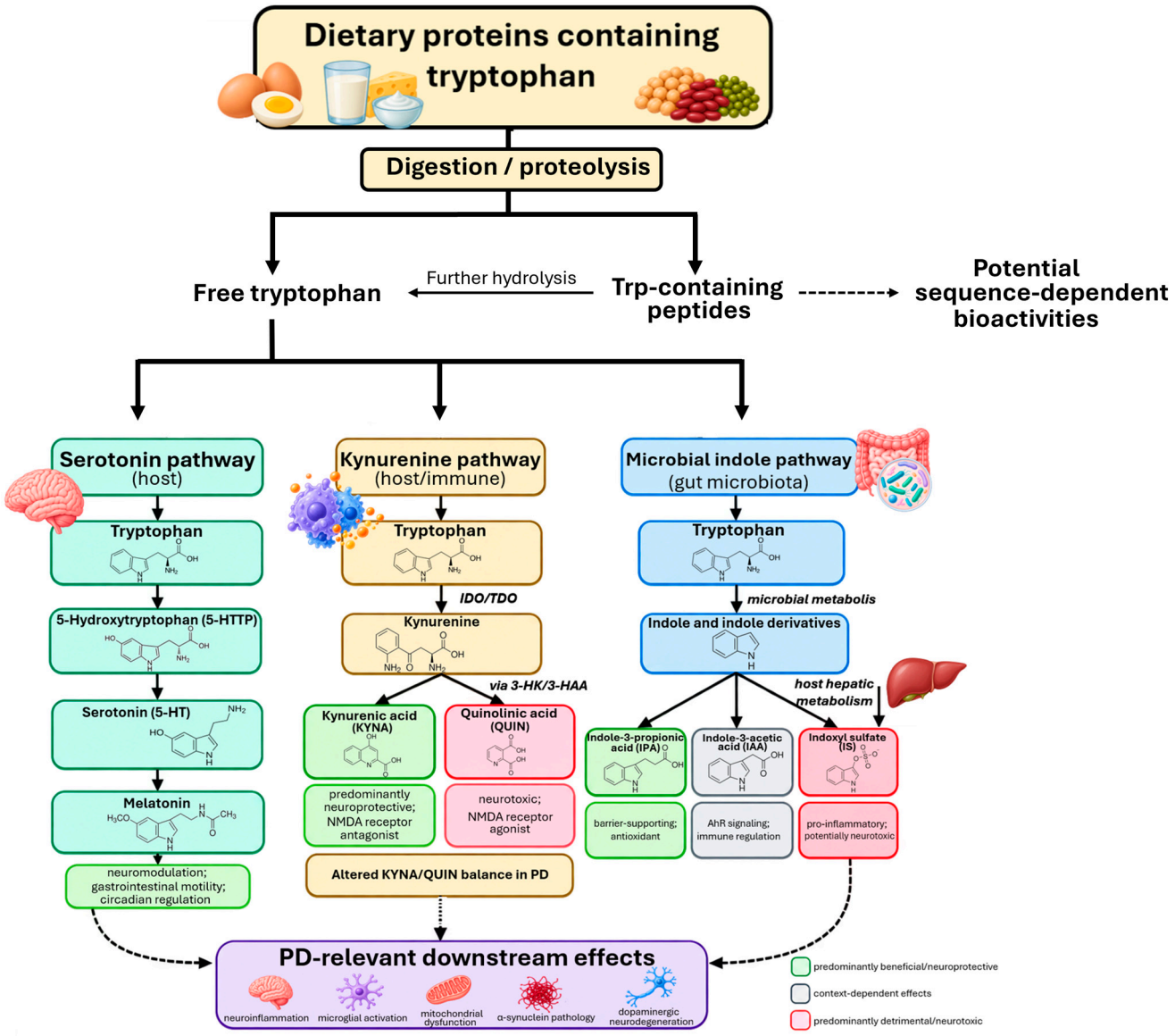


Figure 3. Dietary protein-derived tryptophan and peptides at the host–microbiota interface. Digestion of dietary proteins releases free tryptophan and Trp-containing peptides, which may undergo further hydrolysis or exhibit sequence-dependent bioactivities. Free tryptophan enters the host serotonin and kynurenine pathways or microbial indole pathways. Selected downstream metabolites have context-dependent effects relevant to neurotransmission, barrier function, inflammation, and neuronal homeostasis. The scheme is conceptual; experimental bioactivities do not establish clinical efficacy in PD. Solid arrows indicate the direction of digestion, hydrolysis, or metabolic conversion; intermediate steps may be omitted. Dashed arrows indicate potential sequence-dependent peptide bioactivities or proposed links to PD-relevant downstream effects, rather than direct metabolic conversions.

Nutritional modulation of tryptophan metabolism may therefore involve not only total protein intake but also protein source selection, food processing, and meal composition, which collectively influence microbial access to tryptophan and downstream metabolite profiles relevant to PD pathophysiology.

3.3. Dietary Fat as a Modulator of Microbial Metabolism

Dietary fat quantity and composition may influence gut microbial metabolism by modifying intestinal substrate availability and the bile acid pool, thereby affecting microbial conversion of primary to secondary BAs [25,48]. Within the nutritional framework of this

review, these processes illustrate how dietary exposure can shape microbial metabolic outputs. PD-associated alterations in BA profiles, sphingolipids, and other lipid-related signals, together with their clinical and experimental evidence, are discussed in detail in Section 4.4.

4. Diet-Modulated Microbial Metabolites Beyond Short-Chain Fatty Acids

Beyond SCFAs, microbial metabolism generates a broad spectrum of neuroactive, immunomodulatory, and metabolic signals. Their interpretation in PD requires attention to dietary substrate availability, host metabolism, biological matrix, pharmacotherapy, and disease stage.

4.1. Neuroactive Biogenic Amines

Selected gut microorganisms possess the capacity to produce, transform, or modulate the availability of neuroactive compounds, including GABA, dopamine, serotonin (5-HT), and noradrenaline [16,33,45]. For example, selected bacterial taxa have been reported to possess pathways associated with dopamine production. These microbially associated neuroactive signals may contribute to gut–brain communication through local intestinal, metabolic, immune, and neural mechanisms rather than through direct control of central neurotransmitter concentrations.

Selected kynurenine-pathway metabolites can modulate glutamatergic and α7 nicotinic acetylcholine receptor signaling, thereby influencing excitatory neurotransmission [34]. Histamine may also contribute to PD-relevant neuroinflammatory signaling; experimental evidence indicates that H1 receptor activation can promote microglial activation, oxidative stress, and dopaminergic neuronal toxicity [79].

Understanding how the GM affects these neurotransmitters is essential for elucidating the full complexity of the gut–brain axis.

4.2. Tryptophan-Derived Metabolites

Chronic low-grade inflammation can activate the KP, leading to a metabolic shift from 5-HT synthesis toward KP activation, which may contribute to depressive symptoms in PD [34]. Several studies have reported reduced circulating concentrations of tryptophan and/or kynurenine in patients with PD, although findings across cohorts remain heterogeneous. In an early-stage rotenone-induced PD mouse model, Yan et al. [80] demonstrated significant alterations in multiple serum amino acids (including L-proline, L-alanine, L-serine, L-asparagine, L-threonine, L-glutamine, and L-methionine), which were strongly correlated with gut microbiota composition, particularly *Ruminococcaceae* and *Ruminiclostridium* [80]. In a rat model of PD, Trp supplementation protected against rotenone-induced neurotoxicity and improved motor deficits, likely through activation of the AhR pathway [81]. Genetically proxied abundance of the bacterial genus *Demequina* has been associated with PD risk, with circulating tryptophan proposed as a potential mediator of this relationship [82].

Important Trp-derived metabolites include indole and kynurenine-pathway derivatives such as KYNA, QUIN, 3-hydroxykynurenine (3-HK), indole-3-acetic acid (IAA), and indoxyl sulfate (IS). KYNA is an endogenous antagonist of excitatory glutamatergic signaling, including NMDA receptor activity, and has been associated with potentially neuroprotective effects [34,36]. It may also exert anti-inflammatory effects in the gut. Combined administration of L-kynurenine and probenecid has shown protective effects against 6-hydroxydopamine-induced striatal dopaminergic toxicity in rats [83]. In contrast, QUIN acts as an NMDA receptor agonist and has been associated with excitotoxic and neurotoxic

effects. It can promote reactive oxygen species (ROS) production and interfere with catecholamine biosynthesis. Similarly, 3-HK may enhance oxidative and excitotoxic stress [34]. IAA has been identified as an aberrant urinary metabolite in patients with PD [11], while IS represents another Trp-derived compound that exhibits significant alterations in PD [15]. Elevated urinary IS levels have been reported in patients with PD [37]; however, this finding alone does not establish gut dysbiosis or distinguish altered production from changes in renal handling and urinary excretion. Moreover, the CSF-to-plasma IS ratio has been reported to be higher in patients with PD than in healthy controls, suggesting increased CNS exposure to this metabolite [84].

Experimental studies conducted in the context of chronic kidney disease (CKD) have demonstrated that IS can induce oxidative stress and pro-inflammatory responses in astrocytes and microglia [39]. In a separate CKD-related in vitro study, AST-120 reduced astrocytic inflammatory responses induced by sera from patients with CKD [85]. These findings provide mechanistic context, but their extrapolation to PD remains unvalidated and does not establish therapeutic efficacy of AST-120 in PD. Although elevated urinary IS levels [37] and a higher CSF-to-plasma IS ratio [84] have been reported in PD, these findings represent distinct measurements. Their associations with motor or non-motor symptom severity remain insufficiently established and require further investigation.

Possible reasons for discrepant findings include differences in the metabolites measured and the biological compartments examined [86,87]. Reduced circulating tryptophan or kynurenine should not be interpreted as evidence of uniformly reduced downstream pathway activity, because metabolite concentrations do not directly measure metabolic flux. Studies assessing precursor concentrations therefore provide complementary information to those examining downstream metabolites or metabolite ratios [86,88]. Differences in inflammatory status, nutritional factors, disease stage, medication exposure, and analytical methods may further contribute to between-study variability [86,87]. These factors remain potential explanations rather than established causes of the discrepancies.

To better illustrate the disturbances in Trp metabolism in PD, Figure 3 presents the three main metabolic pathways: the serotonergic, KYN, and indole pathways, along with their characteristic metabolites and their potential neuroprotective or neurotoxic effects.

4.3. Tyrosine- and Phenylalanine-Derived Metabolites

Gut bacterial metabolism of tyrosine can generate p-cresol, which is subsequently conjugated by host sulfation and glucuronidation to form p-cresyl sulfate (PCS) and p-cresyl glucuronide (PCG), respectively. Increased circulating concentrations of PCS and PCG have been reported in patients with PD [41]. PCS may impair neuronal function and exert cytotoxic effects through oxidative stress and pro-inflammatory signaling. In a mouse model, PCG attenuated LPS-induced blood–brain barrier (BBB) disruption, supporting a potential protective effect in this experimental setting [89].

Elevated PCS concentrations have also been reported in individuals with idiopathic REM sleep behavior disorder (iRBD) and in patients with PD and REM sleep behavior disorder (PD-RBD+), suggesting that PCS may represent a circulating metabolic correlate of the proposed body-first PD phenotype [43]. An increased CSF-to-plasma PCS ratio has been reported in patients with PD, suggesting greater CNS exposure to this metabolite [84]. Circulating proteolytic microbial metabolites have also been associated with stool consistency and constipation in patients with PD [42].

Phenylacetylglutamine (PAGln), another host–microbial co-metabolite derived from aromatic amino acid metabolism, has likewise been reported at increased plasma concentrations in patients with PD. Higher plasma PAGln concentrations have been associated with greater motor symptom severity and constipation in patients with PD [41]. Pheny-

lalanine is an upstream precursor of catecholamine biosynthesis through its conversion to tyrosine [45], while microbial metabolism of phenylalanine can generate phenylacetic acid and related metabolites that may contribute to gut–brain metabolic signaling [44].

Possible explanations for discrepant PCS and PAGln findings include differences in biological matrix, constipation severity and intestinal transit, renal function, dietary protein exposure, medication use, and clinical phenotype. Associations with bowel function and RBD-related phenotypes highlight the importance of cohort characteristics [41–43], while CSF-to-plasma measurements address a different question from circulating concentrations alone [84]. These factors should be considered potential contributors to between-study variability rather than established explanations for individual discrepancies. Cross-sectional associations with symptom severity should also not be interpreted as evidence of prognostic validity.

4.4. Bile Acids, Sphingolipids, and Bacterial Lipids

Alterations in sphingolipid and ceramide metabolism have been reported in patients with PD and may be related to disturbances in neuronal membrane homeostasis and mitochondrial function [68]. Lipidomic profiling has also revealed distinct lipid-related metabolic signatures in PD, including sebum-associated alterations that discriminate patients from healthy controls [90]. In addition, decreased long-chain acylcarnitine concentrations have been reported in PD, including in early-stage disease, suggesting their potential utility as candidate diagnostic biomarkers while also indicating disturbances in fatty acid β-oxidation and lipid metabolism [91]. Human studies have reported altered primary and secondary BA profiles in PD [46], including a distinct BA signature in patients with PD and mild cognitive impairment [47]. These observational findings do not establish that specific BAs cause barrier dysfunction or neurodegeneration. Separately, experimental work has implicated microbiota-derived deoxycholic acid (DCA) in BBB dysfunction: DCA administration exacerbated BBB disruption, dopaminergic neurodegeneration, and motor impairment in a rotenone-induced PD model [92].

Collectively, these findings suggest that lipid-related metabolites, including sphingolipids and BAs, may represent candidate biomarkers of PD; however, their potential diagnostic, prognostic, or stratification applications requires separate validation [46,68,90].

Accumulating evidence suggests that bacterial structural components and lipid-related signals, including LPS, PGN-derived fragments, and alterations in ceramide-associated pathways, may contribute to PD-related neuroinflammatory processes, α-Syn aggregation, and neuronal dysfunction.

Lipopolysaccharide (LPS), a component of the outer membrane of Gram-negative bacteria, has been investigated as a potential link between intestinal barrier dysfunction and PD-related inflammation. In a small study of newly diagnosed, untreated patients with PD, increased intestinal permeability correlated with sigmoid mucosal α-Syn staining and markers related to bacterial and endotoxin exposure; these associations did not establish causality [93]. Separately, systemic LPS administration in mice induced persistent neuroinflammation and delayed progressive loss of nigral dopaminergic neurons [94]. In vitro biophysical experiments also demonstrated that LPS can interact with α-Syn and accelerate nucleation and aggregation [95]. These findings support mechanistic plausibility but do not establish that gut-derived LPS initiates or drives PD in humans.

Interactions between α-Syn and sphingolipid-containing membranes may influence both α-Syn aggregation and lipid homeostasis [14]. In addition, sphingomyelin has been identified within Lewy bodies, further supporting a potential link between sphingolipid metabolism and α-Syn pathology [2]. Peptidoglycan (PGN), a major structural component of bacterial cell walls, may contribute to innate immune signaling relevant to PD. PGN-

derived muropeptides are recognized by pattern-recognition receptors, including NOD1 and NOD2, thereby activating innate immune pathways [75]. More broadly, experimental studies indicate that gut microbiota-derived signals can influence blood–brain barrier integrity, neuroinflammation, and PD-related motor phenotypes [73,74]. However, direct evidence linking PGN-derived signaling specifically to human PD remains limited. Thus, PGN-related pathways should currently be regarded as a mechanistically plausible, but incompletely validated, component of microbiota–host signaling in PD.

Taken together, these findings indicate that the biological effects of microbiota-associated metabolites in PD cannot be classified in a strictly binary manner as neuroprotective or neurotoxic. Their impact appears to depend on concentration, biological matrix, site of action, host metabolic context, and disease stage, with individual compounds potentially exerting divergent effects under different experimental or clinical conditions.

4.5. TMAO and Other Emerging Metabolic Signals

In addition to the major classes of metabolites discussed above, several other metabolic signals have been investigated in PD, including trimethylamine N-oxide (TMAO), organic acids such as succinate and lactate, indole derivatives, BAs, caffeine-related metabolites, and histamine. Findings regarding TMAO remain inconsistent across human studies and biological matrices. Some studies have reported higher circulating TMAO concentrations in patients with PD [24,53], whereas others have observed lower circulating or urinary concentrations [13,55,56]. Urine-based studies have also reported reduced TMAO concentrations in patients with PD, with urinary TMAO levels showing an association with disease severity [55]. These apparently bidirectional findings may reflect differences in disease stage, biological matrix, renal handling and excretion, diet and precursor availability, medication exposure, and reverse causality.

These observational inconsistencies should also be considered alongside genetic evidence. A Mendelian-randomization analysis provided suggestive evidence that higher genetically predicted circulating TMAO concentrations were associated with lower odds of motor fluctuations in PD (OR 0.851, 95% CI 0.731–0.990; $p = 0.037$). However, this association did not meet the significance threshold after correction for multiple testing and should not be interpreted as establishing a protective causal effect of TMAO [54]. Thus, the available evidence does not support a uniform disease-associated direction of TMAO change. At present, TMAO should therefore be regarded as a context-dependent metabolic correlate with potential prognostic relevance rather than an established diagnostic or causal biomarker of PD. PD susceptibility, progression-related outcomes, and cross-sectional metabolite differences represent distinct questions; findings concerning one should not be interpreted as direct confirmation or refutation of findings concerning another [13,24,54].

Alterations in other metabolic pathways have also been reported. Increased urinary succinic acid concentrations have been observed in patients with PD and were negatively correlated with disease severity [55], whereas reduced lactate concentrations have been described in treated patients [24]. Disturbances in indole metabolism [53] and BA profiles have likewise been associated with PD, including increased concentrations of selected secondary BAs [46]. In addition, reduced plasma or serum concentrations of caffeine and its metabolites have been reported [96]. Potential links between histamine signaling and mitochondrial dysfunction have been discussed in a review of gut microbial metabolites in PD; however, their relevance to human PD remains uncertain [48].

5. Metabolomics and Multi-Omics at the Nutrition–Microbiota–Metabolism Interface

The advancement of multi-omics technologies, including metagenomics, transcriptomics, proteomics, and metabolomics, has greatly accelerated the characterization of microbiota-derived metabolites and their associations with PD [5,48,58,97]. These integrated approaches provide a multidimensional view of disease-related processes, encompassing microbial composition and functional potential, gene expression, protein profiles, and metabolite patterns [34,59]. Proteomic profiling of cerebrospinal fluid, plasma, and urine has identified candidate biomarkers of early PD, including DOPA decarboxylase (DDC), with findings assessed across independent cohorts and complementary analytical platforms [98].

Analytical platforms used in PD metabolomics include liquid chromatography–mass spectrometry (LC–MS), gas chromatography–mass spectrometry (GC–MS), and nuclear magnetic resonance (NMR) spectroscopy. For example, Dahabiyeh et al. combined LC–MS/MS and GC–TOF MS to investigate serum metabolic profiles in patients with PD and healthy controls [76]. NMR has also been applied to PD biofluids, including plasma profiling using proton NMR spectroscopy [99]. A comparative overview of the principal metabolomic and integrative analytical approaches used in PD research is provided in Supplementary Table S2.

Each metabolomic platform provides complementary analytical coverage but is also subject to methodological limitations that complicate cross-study comparisons. Major challenges include heterogeneity in sample preparation, data acquisition and processing, metabolite annotation, and bioinformatic workflows. Greater methodological standardization and the integration of metabolomics with other omics layers are therefore important for improving reproducibility and obtaining a more comprehensive understanding of microbiota–host metabolic interactions in PD.

In metabolomic research, two primary analytical strategies are commonly distinguished: untargeted and targeted metabolomics. Untargeted metabolomics enables the detection of hundreds to thousands of analytical features across a broad chemical space, although only a subset can typically be confidently annotated or identified as specific metabolites. This approach can reveal previously unrecognized metabolic alterations associated with PD and generate hypotheses regarding disease-related pathways. In contrast, targeted metabolomics focuses on the quantitative determination of predefined metabolites in biological matrices, as exemplified by targeted profiling of caffeine and its downstream metabolites in PD [96]. Interpretation of high-dimensional metabolomic datasets increasingly relies on multivariate statistics, bioinformatics, and machine-learning approaches, which can support feature selection, pattern recognition, disease classification, risk modeling, and integration with other omics layers [97].

Constraint-based microbial community models, such as MICOM, can provide sample-specific simulations of interspecies metabolic interactions and predict the effects of dietary inputs on the production of SCFAs and other microbial metabolites. These predictions can subsequently be compared with experimentally measured metabolomic profiles [100].

In PD research, machine-learning approaches applied to metabolomic datasets, including LC–MS-derived profiles, have been used for case discrimination and for identifying alterations in lipid and amino acid metabolic pathways, including in serum and sebum analyses [90,101,102].

A robust analytical workflow should include appropriate data preprocessing and batch-effect correction, feature selection, and rigorous cross-validation of supervised models. For multi-omics integration, available approaches include DIABLO for supervised integration and feature selection [103], Similarity Network Fusion (SNF) for combining

sample-similarity networks across data types [104], and MOFA+ for identifying latent factors underlying variation across molecular layers [105]. Candidate biomarkers identified in PD should be evaluated in independent cohorts and against other parkinsonian disorders to assess their reproducibility and diagnostic specificity [98,106].

Biological Matrices, Disease Stage, and Preanalytical Confounding

Understanding metabolic differences across the various stages of PD is crucial for identifying candidate biomarkers and elucidating mechanisms underlying disease progression. However, most available studies are cross-sectional in nature, which substantially limits the ability to establish causal relationships [59]. Consequently, there is an urgent need for longitudinal investigations to enable more comprehensive insights into the temporal dynamics of metabolic alterations and their relevance to PD pathogenesis [48,59]. To facilitate comparison across the heterogeneous human evidence base, Supplementary Table S1 provides an evidence map of the principal clinical studies discussed in this review, including study design, sample size, biological matrix, direction of metabolite change, consideration of dietary and medication-related confounding, proposed biomarker application, and qualitative evidence grade.

Reduced plasma concentrations of caffeine and its metabolites have been reported in patients with PD, including those at early disease stages [96], and alterations in TMAO levels have been proposed as a candidate prognostic biomarker rather than an established diagnostic marker [13]. In addition, elevated concentrations of p-cresol sulfate (PCS) have been reported in patients with idiopathic REM sleep behavior disorder (iRBD) as well as in PD patients with REM sleep behavior disorder (PD-RBD+) [43]. These findings indicate the presence of distinct metabolic patterns across PD subtypes, particularly in relation to REM sleep behavior disorder. Collectively, the observed differences are consistent with the "body-first" hypothesis and suggest that plasma metabolites, especially those of gut microbial origin, may serve as candidate prodromal or stratification markers for distinguishing PD-related phenotypes and identifying individuals at prodromal stages. However, these associations are derived primarily from observational cohort studies and should be interpreted as reflecting metabolic stratification and host–microbiota interactions rather than defining discrete biological subtypes or direct causal drivers of PD.

A prospective study identified 13 microbiota-associated metabolites nominally associated with subsequent PD risk; however, none of these associations remained statistically significant after correction for multiple testing, and the findings require independent validation [26]. In a longitudinal study with sampling at baseline, six months, and twelve months, several differences in gut microbial composition between patients with PD and household controls persisted over follow-up, including the underrepresentation of selected SCFA-producing taxa [10]. These findings do not establish whether microbiota changes track clinical progression over longer periods. Higher serum N8-acetylspermidine concentrations were observed in patients with advanced PD compared with early-stage PD [76]. This cross-sectional finding does not establish its ability to predict subsequent motor progression. Overall, alterations in microbiota-derived metabolites such as TMAO, bile acids, and lipid species should be interpreted primarily as correlational metabolic signatures reflecting disease state, host–microbiota interactions, and systemic metabolic remodeling rather than as direct causal drivers of PD.

Metabolite analysis across different biological matrices provides distinct yet complementary information on PD-related metabolic alterations. Fecal metabolomics provides an intestinal metabolic readout enriched in diet-, host-, and microbiota-associated signals, and can therefore offer insight into microbial metabolic activity within the gut. Reduced fecal levels of SCFAs, together with an increased microbial capacity for mucin degradation, have

been frequently reported in patients with PD [5,31]. Plasma and serum metabolomics, in turn, enable the assessment of metabolites circulating throughout the body; studies in this context have revealed alterations in the levels of AAAs and BCAAs, TMAO, lipids, BAs, and caffeine metabolites [14,31,41,53,96].

Metabolomics of CSF, although less extensively characterized, constitutes an important source of information on CNS metabolism [31]. Plasma metabolomics has revealed elevated PAGln concentrations associated with greater motor symptom severity and constipation in patients with PD [41]. Collectively, available studies indicate that metabolite profiles depend on both the biological matrix analyzed and the stage of the disease. Data derived from fecal and plasma samples are currently the most comprehensive, whereas findings from CSF and urine remain fragmentary and often inconsistent. Further comparative analyses in large cohorts are required to determine which biomarkers hold the greatest diagnostic and prognostic potential.

Differences in the concentrations of GM–derived metabolites in patients with PD across feces, plasma, serum, CSF, and urine arise from the complex interplay of intestinal physiology, host metabolism, biological barriers, and PD-specific pathophysiological changes. These differences reflect, among other factors, the permeability of the gut–blood barrier and BBB, thereby justifying the use of multi-sample (multi-matrix) approaches that integrate metabolite analyses from multiple biological matrices such as feces, urine, plasma, and CSF to obtain a broader data spectrum and a more comprehensive view of metabolic processes occurring during disease progression [48,51,84].

Urine represents an attractive biological matrix in metabolomic studies of PD because sample collection is noninvasive and suitable for repeated sampling [107]. Urinary metabolomic studies have identified PD-associated alterations in multiple small-molecule classes, including microbiota-associated metabolites such as indoxyl sulfate [37,107]. These findings support the potential utility of urine for noninvasive biomarker discovery and monitoring of host–microbiota metabolic interactions. However, the diagnostic and prognostic value of urinary metabolite profiles in PD requires further validation in independent and longitudinal cohorts [107].

However, one of the major challenges in metabolomic studies is the lack of standardization of preanalytical procedures. The results are strongly influenced by sampling conditions (e.g., time of day, fasting status, medication use), which can lead to substantial data variability [108,109]. Equally important are sample storage and transport conditions, which may determine metabolite stability and analytical reliability. The absence of unified protocols hampers cross-study comparability and limits the feasibility of large-scale meta-analyses. The development of harmonized preanalytical guidelines therefore constitutes a critical step toward improving the reproducibility of metabolomic studies in PD.

6. Mechanisms Linking Diet-Modulated Microbial Metabolites to Neurodegeneration

6.1. Intestinal and Blood–Brain Barrier Signaling

Microbiota-associated metabolites may influence the CNS through effects on BBB integrity, immune signaling, and, for selected compounds, transport across the barrier [53,110]. The BBB is a key structure regulating the exchange of substances between the bloodstream and the brain, controlling the transport of both nutrients and potentially harmful molecules [8]. Altered BBB integrity has been reported in patients with PD and in experimental models, potentially facilitating the entry of circulating pro-inflammatory factors and metabolites into the CNS and thereby contributing to neuroinflammatory and neurodegenerative processes [25,52,66,110]. Recent experimental multi-omics data indicate that microbiota-derived secondary BAs may contribute to BBB dysfunction in PD. In particular,

DCA aggravated endothelial and tight-junction injury and dopaminergic neurodegeneration in a rotenone-based PD model, providing a mechanistic link between microbial bile acid metabolism and BBB impairment [92].

Bidirectional transport of radiolabeled α-Syn across the BBB has been demonstrated in mice [111]. However, this finding alone does not establish the transport or propagation of pathological α-Syn aggregates in human PD. Altered intestinal barrier integrity has been reported in PD and may facilitate the translocation of microbial products, metabolites, and inflammatory mediators into the systemic circulation. These changes may contribute to systemic inflammation and, in turn, influence BBB integrity and neuroinflammatory processes [66].

6.2. Neuroinflammation, Dopaminergic Neurons, and Mitochondrial Function

GM–derived metabolites and systemic inflammatory processes play a significant role in modulating the function of microglia, dopaminergic neurons, and mitochondria in PD. Their impact encompasses both neuroinflammatory mechanisms and metabolic dysfunctions of neuronal cells.

Experimental evidence indicates that microbiota-related signals and altered metabolite profiles may modulate microglial activation, a key component of neuroinflammation in PD [38,53,66].

Changes in GM composition and metabolite concentrations may promote activation of microglia and astrocytes, contributing to neuroinflammatory signaling. Microglia can internalize extracellular and pathological forms of α-Syn, which may further amplify inflammatory signaling within the CNS. Following α-Syn internalization, activated microglia can release pro-inflammatory cytokines such as IL-1β, IL-6, and TNF-α. These processes may contribute to oxidative stress and neuroinflammation, thereby promoting α-Syn aggregation and dopaminergic neuronal injury [38,53,56]. Moreover, α-Syn aggregation may further enhance microglia-mediated pro-inflammatory signaling, potentially creating a feed-forward inflammatory loop [6,56].

In an MPTP-induced mouse model of PD, sodium butyrate aggravated motor dysfunction, dopaminergic neuronal loss, and glia-mediated neuroinflammation, including increased microglial and astrocytic activation [112]. However, the effects of SCFAs on microglial function appear to be context-dependent, with other studies suggesting potentially modulatory or anti-inflammatory effects [58]. Dietary factors are also influential: a diet rich in BCAAs has been shown to exert a potential anti-inflammatory effect in a mouse model of PD, which may affect microglial function [64].

The loss of dopaminergic neurons in the SNpc and the resulting depletion of dopamine levels in the striatum are hallmark features of PD [3,5,44]. The pathogenesis of this process is complex and involves both mechanisms related to the accumulation of α-Syn and the influence of GM–derived metabolites and systemic inflammation. Aberrant α-Syn accumulation is a central feature of PD [3,5,59]. Experimental studies in rats have demonstrated transport of α-Syn from the intestinal wall to the brainstem via the vagus nerve, supporting a possible gut-to-brain route without establishing this as a universal mechanism in human PD [113].

Certain microbiota-derived metabolites may accelerate dopaminergic neuron degeneration [56]. FuBAs promote α-Syn aggregation, whereas vitamins may exert neuroprotective effects through anti-amyloidogenic, antioxidant, and anti-inflammatory properties [3]. In a human iPSC-derived midbrain organoid model, TMAO induced neurodegeneration-related changes, including loss of dopaminergic neurons and increased pathological phosphorylation of α-Syn at Ser129 [114].

Gut microbial metabolism may also influence the bioavailability and therapeutic effects of levodopa (L-DOPA), the dopamine precursor used in PD treatment; this interaction is discussed in detail in Section 7.

Mitochondrial dysfunction is a central mechanism in the pathogenesis of PD [3,52,56,59], as mitochondria are responsible for cellular energy production, and their impairment leads to reduced energy availability, increased oxidative stress, and activation of apoptotic pathways [3,23,48]. Postmortem analysis of substantia nigra tissue from patients with PD demonstrated reduced mitochondrial respiratory-chain complex I activity compared with matched controls [115]. At the same time, misfolded α-Syn disrupts mitochondrial dynamics, including fusion, fission, and axonal transport of mitochondria, thereby deepening mitochondrial dysfunction and accelerating dopaminergic neuron loss [23].

Metabolite-related interventions have shown distinct effects on cellular survival and mitochondrial function in experimental PD models. Sodium butyrate improved locomotor performance and survival in rotenone-exposed Drosophila, with findings supporting the involvement of HDAC-related mechanisms [116]. Nicotinamide (NAM), a precursor of NAD^+, attenuated nigral dopaminergic cell loss and striatal dopamine depletion in mouse MPTP models [117]. Ursodeoxycholic acid (UDCA) rescued mitochondrial dysfunction in PD-related cellular models, including LRRK2-mutant fibroblasts [118]. Separately, tauroursodeoxycholic acid (TUDCA) preserved ATP levels and mitochondrial function and reduced neuroinflammation in an MPTP mouse model [119]. These findings concern distinct experimental outcomes and should not be interpreted as evidence that all four compounds promote mitophagy or exert equivalent effects. In an enteroendocrine cell model, conditioned medium from Akkermansia muciniphila induced RyR-mediated Ca^{2+} release, increased mitochondrial Ca^{2+} uptake and ROS generation, and promoted α-Syn aggregation; these effects were attenuated by buffering mitochondrial Ca^{2+} [120].

In an 8-week pilot randomized trial, a ketogenic diet produced greater improvement in non-motor symptoms than a low-fat diet, but no significant between-group differences were observed in motor outcomes [121]. Thus, mitochondrial dysfunction in PD arises from a complex interplay of environmental toxins, aberrant α-Syn, microbiota-derived metabolites, and dietary factors, which together drive dopaminergic neuron loss and disease progression.

6.3. Epigenetic and Post-Transcriptional Regulation and Neurotransmission

Epigenetic modifications, which alter gene expression without changing the DNA sequence, play an important role in the pathogenesis of PD. GM–derived metabolites, including butyrate, are linked to epigenetic changes that may influence depressive symptoms in patients with PD [2]. There is also a strong interaction between genetic and epigenetic factors in the disease [7]. The HDAC inhibitor phenylbutyrate increased DJ-1 expression and exerted protective effects in cellular and animal models of PD [122]. Separately, in rotenone-treated PC12 cells, sodium butyrate increased histone acetylation at the promoter of peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α), upregulated PGC-1α expression, and enhanced autophagy, accompanied by reduced α-Syn protein levels [123]. This reduction should be distinguished from suppression of α-Syn gene transcription, as the reported mechanism involved autophagy-mediated protein turnover. Epigenetic regulation of the gut–brain axis integrates microbial genes, brain function, and behavior, underscoring the role of the microbiota in modulating neurodegenerative processes [124].

Beyond chromatin-level regulation, microRNAs (miRNAs) provide an additional layer of post-transcriptional control by modulating target mRNA stability and translation. Their relevance to PD is supported by longitudinal profiling of circulating small noncoding RNAs, which identified disease-associated signatures and regulatory modules related to

progression [125]. Noncoding RNA networks therefore represent a complementary research direction for understanding PD-related gene regulation, although disease-associated expression changes do not alone establish causality [126].

A further distinction concerns microRNA-encoded peptides (miPEPs), which are translated from short open reading frames within certain primary miRNA transcripts, and other micropeptides encoded by transcripts previously annotated as noncoding. These molecules should not be confused with mature miRNAs or with peptides released through dietary protein digestion. Experimental evidence indicates that miPEPs can have regulatory functions, but enhancement of their corresponding miRNA expression is not a universal mechanism in human cells [127]. As discussed by Velarde-Salcedo et al. (2026), these emerging peptide classes broaden investigation of diet–microbiome–brain communication. Their specific contribution to diet- or microbiota-mediated regulation in PD remains to be established, and they should currently be presented as candidates for mechanistic investigation rather than validated mediators or therapeutic targets [77].

The GM and its metabolites may influence neurotransmission through multiple indirect mechanisms, including modulation of precursor availability, peripheral metabolism, immune signaling, and neural pathways. Dopamine is a key neurotransmitter in both the central and peripheral nervous systems and plays an essential role in cognition, motivation, and voluntary movement; however, direct regulation of central dopamine levels by the gut microbiota in humans remains insufficiently established. Disturbances in dopamine, glutamate, serotonin, GABA, acetylcholine, and glycine signaling are associated with the neurological and non-motor manifestations of PD [2,25,44].

AAAs, which serve as precursors of neurotransmitters such as serotonin, dopamine, and noradrenaline, play a crucial role in motor control and cognitive function [34,45]. The GM may influence the metabolism and availability of amino acid precursors and, through the activity of selected microbial taxa, contribute to the production or modulation of neuroactive compounds such as GABA, dopamine, serotonin, and noradrenaline [8,16,25,56]. Selected strains within Lactobacillaceae and the genus *Bifidobacterium* possess glutamate decarboxylase activity and can convert glutamate to GABA; however, this capacity is strain-dependent and should not be generalized to entire bacterial genera [8]. In selected experimental models, specific probiotic strains have altered central dopamine levels. For example, oral administration of *Lactobacillus plantarum* PS128 increased striatal dopamine concentrations in rotenone-treated mice [128]. Changes in amino acid concentrations influence the balance between excitatory and inhibitory neurotransmitters, thereby modulating nervous system function [8].

Collectively, these findings indicate that diet-modulated microbial signals may converge on several PD-relevant processes, including barrier integrity, neuroinflammation, mitochondrial homeostasis, epigenetic regulation, and neurotransmission. However, the magnitude and direction of these effects are context-dependent and likely reflect interactions among microbial composition and function, host metabolism, dietary exposure, pharmacotherapy, and disease stage.

7. Nutrition–Microbiota–Drug Interactions: Levodopa as a Translational Example

Levodopa, also known as L-3,4-dihydroxyphenylalanine (L-DOPA), is a dopamine precursor used for symptomatic treatment of PD. The terms levodopa and L-DOPA refer to the same compound; L-DOPA is used consistently below. In this section, microbial L-DOPA metabolism refers primarily to bacterial conversion of the administered drug to dopamine within the intestinal lumen, which may reduce its availability for absorption [129]. Dietary factors can influence L-DOPA bioavailability through several mechanisms, including compe-

tition between dietary large neutral amino acids and L-DOPA for intestinal absorption and transport across the blood–brain barrier. In parallel, gut bacteria expressing tyrosine decarboxylase (TDC), particularly enterococci, can convert L-DOPA to dopamine in the intestinal lumen, thereby potentially reducing the amount of drug available for absorption [129]. Although dietary protein intake, meal composition, and protein distribution can influence L-DOPA pharmacokinetics, direct evidence that specific dietary patterns selectively expand TDC-positive bacterial populations and thereby modify L-DOPA metabolism in humans remains limited.

Importantly, the peripheral aromatic L-amino acid decarboxylase inhibitor carbidopa does not efficiently inhibit bacterial TDC, which remains capable of converting L-DOPA to dopamine in the intestinal lumen [129]. Consequently, bacterial L-DOPA decarboxylation may contribute to interindividual variability in drug bioavailability despite concomitant treatment with carbidopa [5]. This microbiota-mediated pathway therefore represents a potentially relevant component of L-DOPA pharmacokinetics. However, randomized controlled trials have not yet established whether dietary protein manipulation modifies L-DOPA bioavailability specifically through changes in microbial TDC activity in humans.

Experimental studies have provided proof-of-concept that bacterial L-DOPA metabolism can be pharmacologically targeted. Van Kessel et al. demonstrated that gut bacterial tyrosine decarboxylases, particularly those expressed by Enterococcus spp., decarboxylate L-DOPA to dopamine and are not effectively inhibited by carbidopa [129]. In a separate study, Maini Rekdal et al. demonstrated that (S)-α-fluoromethyltyrosine (AFMT) inhibits bacterial L-DOPA decarboxylation, providing experimental proof-of-concept for targeting microbial drug metabolism [130]. Other microbiome-targeted approaches under investigation include inhibition of downstream bacterial dopamine metabolism, modulation of TDC-harboring bacterial populations, and strategies aimed at altering intestinal microbial ecology [5,8,36]. These approaches remain predominantly experimental and require further validation before clinical application.

Translation of microbiota-targeted modulation of L-DOPA metabolism into clinical practice will require careful evaluation of efficacy, safety, interindividual microbiome variability, and potential interactions among diet, microbial metabolism, and pharmacotherapy. Candidate pharmacomicrobiomic markers may include intestinal *tdc* gene abundance and metabolite ratios reflecting L-DOPA conversion; however, their clinical utility has not yet been established and may be influenced by meal timing, dietary protein intake, medication schedule, intestinal transit, and other preanalytical and biological factors [8,36].

From a nutritional perspective, protein redistribution, with a greater proportion consumed in the final main meal, may be considered for selected patients receiving L-DOPA who experience motor fluctuations. This strategy concerns the timing and distribution of protein intake rather than a reduction in total daily protein consumption; adequate overall protein intake should be maintained [131]. Whether replacing animal with plant protein sources or increasing dietary fiber can modify TDC-positive bacterial populations and thereby improve L-DOPA bioavailability in humans remains insufficiently established. Future studies integrating detailed dietary assessment, microbiome profiling, and pharmacokinetic measurements are needed to determine whether such interventions can reproducibly modify microbial L-DOPA metabolism and therapeutic response.

Overall, the interaction between diet, gut microbial metabolism, and L-DOPA provides a clinically relevant example of the potential integration of precision nutrition with pharmacomicrobiomics. Current evidence supports a role for dietary protein distribution and microbial TDC activity in influencing L-DOPA availability, whereas direct diet-mediated modulation of TDC-positive microbial populations remains an emerging research area.

Better characterization of these interactions may ultimately support more individualized approaches to L-DOPA therapy in PD.

8. Nutrition- and Microbiome-Targeted Interventions

8.1. Dietary Patterns and Human Intervention Trials

Dietary patterns such as the Mediterranean, MIND, and ketogenic diets have attracted increasing interest in PD because they may influence inflammatory status, oxidative stress, metabolic homeostasis, and gut microbial function. However, the level of evidence differs substantially among these dietary approaches. For the MIND diet, available evidence is predominantly observational. Higher adherence to MIND-type dietary patterns has been associated with a lower risk of parkinsonism and slower progression of parkinsonian features [132], later age at PD onset [133], and lower patient-reported symptom burden [134], but these associations do not establish causality.

Randomized dietary-intervention studies provide more direct evidence for Mediterranean-style dietary approaches. In a single-center randomized clinical trial involving 80 patients with idiopathic PD, Paknahad et al. compared a Mediterranean diet with a control diet over 10 weeks and reported improvements in cognitive performance in the intervention group [135]. In a related report from the same research program, Mediterranean-diet intervention was associated with increased serum total antioxidant capacity and lower total UPDRS scores, although no significant improvement in the motor component of UPDRS was observed [136]. The relatively small sample size and single-center design limit the generalizability of these findings.

More recent trials have produced mixed results. In an 8-week parallel randomized controlled trial including 36 participants with PD and constipation, Rusch et al. compared a Mediterranean diet plus standard constipation care with standard care alone. Constipation symptoms improved in both groups, with no significant between-group difference. The Mediterranean-diet group achieved higher dietary fiber intake, while fecal zonulin did not differ between groups and fecal calprotectin showed only a borderline reduction, indicating that gastrointestinal and inflammatory benefits remain uncertain [137].

Ketogenic and Mediterranean–ketogenic interventions have also been investigated. In a pilot randomized controlled trial comparing a ketogenic diet with a low-fat diet over 8 weeks, both groups showed improvements in MDS-UPDRS scores, whereas the ketogenic group demonstrated a greater improvement in non-motor symptoms, with no clear between-group advantage for motor outcomes [121]. More recently, Tosefsky et al. evaluated two 8-week Mediterranean-based ketogenic interventions in a randomized crossover study of 52 participants. Only 63% completed both intervention phases, and objective adherence and ketosis were variable. Small improvements in selected MDS-UPDRS outcomes were observed primarily after the Mediterranean diet supplemented with medium-chain triglycerides, despite inconsistent achievement of ketosis. These findings emphasize feasibility and adherence challenges and should be regarded as preliminary rather than evidence of established clinical efficacy [138].

Overall, current human intervention studies suggest that Mediterranean-style and ketogenic dietary approaches may influence selected clinical, metabolic, and gastrointestinal outcomes in PD, but the evidence remains limited by small sample sizes, short intervention periods, heterogeneity of endpoints, incomplete adherence, and inconsistent between-group effects. Accordingly, these dietary patterns should currently be regarded as promising research strategies rather than established disease-modifying or precision-nutrition interventions. Selected randomized dietary-intervention trials are summarized in Table S3.

8.2. Probiotics, Prebiotics, Postbiotics, and Food-First Strategies

Modulation of the GM using probiotics, prebiotics, and postbiotics represents a promising, albeit still developing, adjunctive strategy in the treatment of PD. Probiotics are live microorganisms that, when administered in adequate amounts, confer a health benefit on the host. In experimental and clinical studies, probiotics have been investigated for their potential to modulate inflammatory responses, support intestinal barrier integrity, and influence microbial metabolite production. Experimental models have demonstrated that *Bifidobacterium breve* CCFM1067 alters the SCFA profile, reduces the expression of inflammatory markers, and enhances anti-inflammatory responses [1,33]; *Clostridium butyricum* promotes mitophagy and exerts neuroprotective effects [33,60]; while *Lactobacillus plantarum* PS128 reduces neuroinflammation and α-Syn aggregation in the brain and gut [58]. Multistrain formulations increase butyrate production, supporting dopaminergic neuron survival in MPTP/rotenone toxicity models [25,59]. In addition, probiotics may modulate tryptophan and BA metabolism, further influencing the microbiota–gut–brain axis [25,33,59].

Prebiotics are substrates selectively utilized by host microorganisms that confer a health benefit. Their intake may promote favorable changes in gut microbial composition and function and may increase the production of SCFAs [62]. In experimental studies, oligofructose modulated microglial activity and alleviated motor deficits, likely through immunometabolic mechanisms [19,58,62]. Postbiotics, defined as preparations of inanimate microorganisms and/or their components that confer a health benefit on the host, may offer greater stability and standardization potential than live microbial preparations. In the context of PD, however, their application remains poorly explored, and evidence for metabolic or immunomodulatory effects is still limited [15,60].

These interventions may act through partially overlapping mechanisms, including modulation of SCFA production, signaling through FFAR2, FFAR3, and HCAR2, regulation of HDAC activity, effects on intestinal barrier function and lipopolysaccharide translocation, and indirect modulation of gut–brain signaling. The relative contribution of these pathways is likely to depend on the specific intervention, microbial composition, and host context.

Despite the growing body of preclinical data, clinical evidence remains limited due to small sample sizes, short follow-up periods, and lack of protocol standardization. Interpretation is further complicated by differences in formulation composition and dosage, duration and route of administration, and patient heterogeneity (diet, pharmacotherapy, PD stage, gastrointestinal symptom phenotype). Additional challenges include the selection of objective endpoints (fecal/plasma metabolomics, gut barrier integrity markers, inflammatory profiles) and control of confounding factors (timing of protein intake relative to L-DOPA, antibiotic therapy).

Although microbiota-based interventions are considered relatively safe, caution is warranted in high-risk populations such as immunosuppressed patients or those with severe dysbiosis. Further well-designed randomized trials with standardized protocols (strain composition, dosing, inclusion criteria, clinical and omics endpoints) are required to identify responsive populations, define biomarkers of response, and establish long-term efficacy and safety profiles. Until more robust clinical evidence becomes available, integration of pro-, pre-, or postbiotic interventions with individual clinical phenotypes and microbiota–metabolomic profiles should be regarded as a research-oriented framework rather than an established therapeutic strategy [32].

Habitual dietary patterns can influence the availability of microbial substrates and thereby modulate the production of microbiota-derived metabolites with potential neurobiological relevance. Direct supplementation of selected metabolites and dietary modulation of their endogenous production represent complementary experimental and translational approaches. In PD, food-based strategies may therefore provide one potential framework

for influencing microbial metabolic outputs and downstream immune, mitochondrial, and neuronal pathways [48].

Microbiota-associated vitamin metabolism may contribute to host coenzymatic and redox pathways relevant to PD. Vitamin K2 has been investigated for its potential effects on α-Syn fibrillization, while B vitamins, including thiamine (B1) and pyridoxine (B6), participate in bioenergetic and one-carbon metabolic pathways [3,56,58]. In selected clinical contexts, such as L-DOPA-associated hyperhomocysteinemia, targeted vitamin supplementation may be considered, although its use should depend on individual nutritional status, biochemical findings, and potential drug–nutrient interactions.

SCFAs, including acetate, propionate, and butyrate, have been implicated in the regulation of intestinal barrier integrity, glial activity, and cellular energy metabolism through mechanisms involving acetyl-CoA availability and FFAR2/FFAR3/HCAR2 signaling [15,48,62,66]. Butyrate can also exert epigenetic effects through HDAC inhibition [25]. However, the biological effects of SCFAs appear to be context-dependent, as preclinical studies have reported both potentially beneficial and adverse effects on neuroinflammatory and motor phenotypes [58].

Other metabolite-related strategies under investigation include modulation of BCAA availability, taurine metabolism, and ketone body production. In experimental PD models, BCAAs have been associated with improved motor parameters and reduced microglial reactivity [64,139], although their interaction with L-DOPA transport warrants consideration because both BCAAs and L-DOPA use large neutral amino acid transport systems. Dysregulated taurine metabolism associated with gut microbiota alterations has been reported in a mouse model of PD [140]; this observational finding does not establish the efficacy of taurine supplementation. Ketone bodies, particularly β-hydroxybutyrate, have also demonstrated anti-inflammatory and neuroprotective effects in experimental settings, while ketogenic dietary strategies may additionally alter gut microbial composition [33,61]. Their clinical relevance in PD, however, requires further validation.

Collectively, microbiota- and metabolite-targeted approaches represent emerging research directions in PD, encompassing supplementation with selected metabolites, dietary modulation of microbial metabolic pathways, and metabolic interventions such as ketogenic strategies. Their clinical translation will require validation of efficacy and safety, identification of appropriate biomarkers and responsive patient subgroups, and confirmation in well-designed multicenter randomized controlled trials [25,48,62].

8.3. Fecal Microbiota Transplantation and Emerging Ecosystem-Level Approaches

Fecal microbiota transplantation (FMT) involves the transfer of processed fecal material from a carefully screened healthy donor to a recipient, with the aim of modifying the recipient's gut microbial community. In PD, the rationale for FMT is based on its potential to influence several microbiota-related processes, including the abundance of SCFA-producing bacteria, intestinal barrier function, pro-inflammatory signaling, neuroactive metabolite profiles, and gut motility [5,16,59,141,142]. These changes may, in turn, affect neuroinflammatory and neurotransmitter-related pathways, although their relevance to clinical outcomes in PD remains uncertain.

In animal models of PD, FMT from healthy donors has been associated with improvements in motor phenotypes, alterations in gut microbial composition, reduced inflammatory markers, and changes in striatal dopamine and serotonin concentrations [5,16,141,143]. Experimental studies have also reported changes in p-cresol concentrations and modulation of TLR4/TNF-α-related signaling following FMT [6,60,144], supporting a potential effect on microbiota-associated inflammatory pathways.

Randomized trials of FMT in PD have produced mixed results. Cheng et al. (2023) randomized 56 patients to oral FMT capsules or placebo; 54 completed the trial. Assessments over 12 weeks showed a favorable group-by-time effect on total MDS-UPDRS scores (B = −6.56; 95% CI −12.98 to −0.13), together with gastrointestinal improvements [145]. In the double-blind phase 2 GUT-PARFECT trial, Bruggeman et al. (2024) assigned 46 patients to nasojejunal healthy-donor or autologous FMT. The primary outcome, change in off-medication MDS-UPDRS III at 12 months, favored donor FMT, with mean improvements of 5.8 versus 2.7 points [146].

Conversely, the multicenter, double-blind trial by Scheperjans et al. (2024), which randomized 48 patients and included 45 in the analysis, found no superiority of single-dose colonoscopic FMT over placebo for the primary endpoint of change in MDS-UPDRS I–III at six months [147]. Similarly, Figura et al. (2026) randomized 59 patients to colonoscopic donor or autologous FMT and found no significant between-group difference in off-medication MDS-UPDRS III at 12 months, although selected non-motor outcomes improved at some time points [148]. In contrast, Zhang et al. (2026) randomized 72 drug-naïve patients to repeated donor or autologous FMT; 66 completed follow-up. At 35 weeks, donor FMT improved UPDRS III scores (−3.8 versus +0.1 points), constipation, and quality of life [149]. These divergent findings underscore the need to distinguish single-dose from repeated-treatment protocols, account for medication exposure and comparator choice, and avoid interpreting microbiota changes as evidence of consistent clinical efficacy.

Efficacy and durability of engraftment and functional integration of donor microorganisms depend on protocol factors: donor selection (including "super-donors"), material preparation (fresh vs. frozen, anaerobic processing), route of administration (colonoscopy, enteric capsules, upper GI delivery), dosing intensity and schedule, and recipient preparation (e.g., bowel cleansing, antibiotics). In PD, donor microbiota functional characteristics, including the capacity for L-DOPA metabolism and the production of SCFAs, tryptophan-derived metabolites, and bile acids, may be relevant to treatment response and host metabolic phenotype [5,16,59]. However, these features have not yet been validated as criteria for donor selection or predictors of clinical response to FMT.

Although preliminary findings are of interest, FMT remains an experimental intervention in PD. Major limitations include the lack of standardized protocols, small and heterogeneous study populations, difficulties with blinding, uncertain durability of engraftment, and the need for rigorous safety monitoring. Reported adverse events associated with FMT include transient gastrointestinal symptoms as well as rare but potentially serious complications related to transmission of infectious agents, underscoring the importance of stringent donor screening and recipient monitoring [32,58,59,143].

Future evaluation of FMT in PD will require multicenter randomized controlled trials with clearly defined clinical and pharmacomicrobiomic endpoints, including metagenomic and metabolomic profiles, gut barrier markers, inflammatory biomarkers, and measures of engraftment durability. Comparative studies with other emerging microbiota-targeted approaches, such as defined bacterial consortia and postbiotic interventions, may also help clarify the relative advantages and limitations of these strategies [5,16,32,59].

9. Limitations of the Current Evidence

Current evidence on microbiota–metabolite interactions in PD is constrained by several methodological limitations. Many studies are based on relatively small and clinically heterogeneous cohorts, reducing statistical power and limiting the generalizability of reported associations. Comparability across studies is further complicated by the use of different biological matrices, including feces, plasma, serum, and CSF, as well as diverse analytical platforms such as LC–MS, GC–MS, and NMR, each providing distinct metabolomic cover-

age and being affected by different preanalytical and analytical sources of variability. For example, NMR spectroscopy offers high reproducibility but lower sensitivity than MS-based approaches, which limits the detection of low-abundance metabolites [150].

Methodological heterogeneity extends to sample collection, processing, storage, analytical workflows, and bioinformatic processing, contributing to substantial inter-study variability and limiting direct comparison and replication of findings. Consequently, candidate metabolomic biomarkers identified in individual cohorts frequently require independent validation, and both the magnitude and direction of reported associations may vary across studies. Differences in diet, medication use, disease stage, gastrointestinal phenotype, and other host-related factors further complicate interpretation and may partly account for inconsistencies between cohorts.

Geographic and ethnic diversity is another limitation. Much of the available evidence comes from cohorts recruited in Europe and East Asia, while other populations remain underrepresented. Recruitment location should not be equated with ethnicity, which is not consistently reported. Differences in habitual diet, environmental exposures, medication use, and host genetic background may affect microbiota composition and metabolite profiles, limiting the transferability of candidate biomarkers and nutritional strategies. Validation in geographically diverse cohorts with clearly reported ethnicity and dietary context is therefore needed.

Addressing these limitations will require large, multicenter studies based on harmonized preanalytical and analytical protocols, standardized collection of dietary and medication data, and well-characterized, diverse patient populations. Such efforts are essential to distinguish reproducible PD-associated metabolic signatures from cohort-specific or method-dependent effects and to establish biomarkers with potential diagnostic, prognostic, or stratification value.

10. Research Priorities for Precision Nutrition in Parkinson's Disease

A major challenge in current microbiome and metabolomic research in PD is the predominance of cross-sectional study designs, which limits causal inference and complicates differentiation between factors associated with disease susceptibility and those arising as consequences of disease progression or treatment. Prodromal and early PD features, including constipation, dysphagia, and hyposmia, as well as exposure to dopaminergic therapy, may themselves alter dietary behavior, gastrointestinal physiology, microbiota composition, and metabolic profiles, thereby contributing to reverse causality. Addressing this limitation will require large prospective cohorts with longitudinal sampling extending from prodromal stages through diagnosis and disease progression, combined with harmonized protocols, deep clinical phenotyping, and standardized assessment of dietary intake and medication exposure. Such studies may help identify microbiota–metabolite signatures that precede clinical PD and distinguish potential risk-associated markers from secondary disease- or treatment-related changes.

Although SCFAs and other microbiota-associated metabolites have been linked to PD-relevant biological pathways, their concentration–response relationships, biological variability, and distribution across compartments remain poorly characterized. Reported metabolite concentrations in feces, blood, and CSF vary substantially across studies, and it remains unclear to what extent these differences reflect disease-related alterations, dietary exposure, intestinal transit, microbiota composition, host metabolism, or methodological variability. Standardized longitudinal multi-matrix studies are therefore needed to clarify relationships among intestinal metabolite production, systemic exposure, central availability, biological activity, and clinical phenotype. Particular attention should be given not only to

SCFAs but also to tryptophan-derived metabolites, secondary BAs, aromatic amino acid derivatives, and other microbial–host co-metabolites implicated in PD.

Microbiome composition and function are highly dynamic and influenced by diet, medication exposure, and host-related factors. Integrating metagenomic, metatranscriptomic, proteomic, and metabolomic data with detailed clinical and nutritional information may provide a more comprehensive view of microbiota–host interactions in PD. Computational frameworks linking microbial taxa, metabolic pathways, and metabolite profiles can help identify functionally relevant associations and generate mechanistic hypotheses. Constraint-based metabolic modeling may further be used to predict microbial metabolic capabilities and metabolite fluxes, but such predictions require experimental and clinical validation before they can inform dietary or microbiota-targeted interventions. Standardization of data acquisition, preprocessing, batch correction, model reporting, and data sharing will be essential to improve reproducibility and cross-cohort comparability.

Complementary experimental platforms will also be important for mechanistic validation. Organoids, organ-on-a-chip systems, and other advanced in vitro models may help investigate bidirectional gut–brain signaling and permit controlled evaluation of microbiota- and metabolite-related effects on epithelial, immune, and neuronal processes. These approaches should be integrated with appropriately designed in vivo models and human studies rather than regarded as substitutes for clinical validation. Improvements in analytical sensitivity, particularly for low-abundance metabolites in CSF, together with parallel blood measurements, may further clarify central–peripheral metabolite relationships and improve interpretation of microbiota-associated metabolic signals relevant to the CNS.

From a translational perspective, probiotics, postbiotics, and microbiota transplantation remain investigational approaches in PD, and their efficacy and safety require confirmation in adequately powered, well-controlled clinical trials. Other emerging strategies include modulation of the kynurenine pathway and other microbiota-associated metabolic pathways; however, their clinical relevance remains to be established. In parallel, metabolomic and multi-omics profiling may ultimately contribute to patient stratification and identification of biologically distinct subgroups, although such applications require prospective validation before they can inform treatment selection or personalized nutritional interventions.

Future biomarker studies should clearly distinguish among diagnostic, prognostic, and predictive applications. Diagnostic biomarkers may support disease identification or differentiation from related disorders, prognostic biomarkers may provide information on disease progression or complication risk, whereas predictive biomarkers may help identify variation in treatment response, including potential microbiota-related effects on L-DOPA bioavailability. Maintaining this functional distinction will improve the interpretation, validation, and translational assessment of candidate microbiota- and metabolite-based biomarkers in PD. Collectively, these research priorities may strengthen causal inference, improve the reproducibility of microbiome–metabolome findings, and provide a more rigorous basis for evaluating nutrition- and microbiota-informed strategies in future PD research.

Operationalizing Precision Nutrition: A Proposed Research Framework

The following framework is proposed for hypothesis-testing rather than clinical implementation. Candidate stratification variables should combine clinical phenotype, dietary exposure, and paired microbial and metabolic measurements. Relevant clinical features include constipation severity, disease stage, nutritional status, and motor fluctuations, together with medication and laxative use. Habitual fiber and protein intake should be assessed alongside these features. Candidate biological measures include fecal SCFAs and

microbial functional pathways, complemented by fasting plasma PCS and PAGln where protein-related microbial metabolism is investigated. Taxa such as Faecalibacterium and Roseburia may provide contextual information, but their abundance should not be treated as a direct measure of metabolic activity or as a validated treatment-selection criterion [27,41].

For an initial fiber-focused trial, participants could be stratified by constipation severity and baseline fiber intake, while metabolite concentrations and microbial functional features are retained as continuous exploratory modifiers. No universal metabolite or taxon cut-offs are currently established for selecting dietary treatment in PD. Two baseline stool samples and a fasting blood sample could be collected during a two-week run-in, with repeat paired sampling at the end of the intervention. Sampling should be standardized relative to meals and medication dosing, with renal function, stool consistency, recent antibiotic exposure, and medication changes documented.

An illustrative design would be a 12-week, parallel-group randomized trial comparing a dietitian-led Mediterranean-style, fiber-enriched intervention with an attention-matched control receiving standard nutritional advice. Both groups would continue usual PD treatment and standardized constipation care. Randomization could be stratified by constipation severity and baseline fiber intake. A prespecified primary endpoint could be change in a validated constipation symptom score; secondary endpoints could include complete spontaneous bowel movements, quality of life, dietary adherence, and adverse events. Fecal SCFAs, plasma metabolites, and microbial pathways would be exploratory mechanistic endpoints. Sample size should be calculated from the primary clinical endpoint, and any treatment-by-baseline-biomarker interactions should be prespecified and considered exploratory unless adequately powered. This design builds on existing dietary-intervention research but does not assume efficacy, given the mixed findings of previous PD trials [137]. A subsequent trial would be required to determine whether biomarker-guided dietary allocation improves outcomes compared with the same dietary intervention delivered without biomarker guidance.

Before clinical use, candidate biomarkers require analytical validation, including precision, accuracy, stability, and interlaboratory reproducibility, followed by external clinical validation for a clearly defined context of use. A marker associated with symptom severity is not necessarily predictive of dietary response. Treatment-selection claims require evidence that baseline biomarker status modifies the comparative effect of an intervention, while clinical utility requires evidence that using the biomarker improves patient outcomes [151].

Ethical safeguards should include prospective trial registration, ethics committee approval, informed consent for biological sampling and secondary data use, and protection of microbiome and clinical data [152]. Within this proposed framework, dietary supervision should prioritize adequate energy and protein intake and monitor weight loss, gastrointestinal intolerance, and changes in motor control. Unvalidated metabolic profiles should not be presented to participants as diagnostic results or established dietary prescriptions. Recruitment across diverse populations and consideration of food affordability and accessibility would also be important for evaluating equitable implementation.

11. Conclusions

Beyond SCFAs, tryptophan metabolites, aromatic amino acid derivatives, bile acids, and other microbiota-associated signals broaden understanding of the diet–microbiota–metabolite axis in PD. These pathways offer candidate biomarkers and mechanistic targets, but their interpretation depends on biological matrix, dietary exposure, medication use, disease stage, and host characteristics. Current evidence remains predominantly observational or preclinical and does not establish metabolite-guided dietary prescriptions or disease-modifying effects.

Clinical translation requires standardized longitudinal studies, external biomarker validation, and adequately powered dietary-intervention trials. Integrating dietary assessment, microbial functional profiling, metabolomics, and clinical phenotyping may support future patient stratification and hypothesis-testing toward precision nutrition. The proposed framework should therefore be regarded as a research agenda rather than an established approach to individualized PD treatment.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/app162211317/s1. **Table S1.** Evidence map of principal human studies investigating microbiota-associated metabolites, metabolomic signatures, and dietary interventions in Parkinson's disease; **Table S2.** Overview of commonly applied metabolomic and integrative analytical approaches in Parkinson's disease research, including representative biological matrices, principal strengths, and major limitations; **Table S3.** Selected randomized dietary-intervention trials in Parkinson's disease.

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Abbreviations

The following abbreviations are used in this manuscript:

PD	Parkinson's disease
GM	gut microbiota
SCFAs	short-chain fatty acids
CNS	central nervous system
ENS	enteric nervous system
BBB	blood–brain barrier
LPS	lipopolysaccharide
KP	kynurenine pathway
KYNA	kynurenic acid
QUIN	quinolinic acid
TMAO	trimethylamine N-oxide
FMT	fecal microbiota transplantation
LC–MS	liquid chromatography–mass spectrometry
GC–MS	gas chromatography–mass spectrometry
NMR	nuclear magnetic resonance
CSF	cerebrospinal fluid
L-DOPA	levodopa
TDC	tyrosine decarboxylase

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